IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Christopher Meade *et al.*	Examiner: Phyllis G. Spivak
Serial No.:	10/614,362	Group Art Unit: 1614
Filed:	July 7, 2003	Docket: 1/1363
Customer No.: 28501		Confirmation No.: 7889

For: PHARMACEUTICAL COMPOSITIONS BASED ON NEW ANTICHOLINERGICS AND NK1 RECEPTOR ANTAGONISTS

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY UNDER 37 C.F.R. § 1.116 IN RESPONSE TO THE DECEMBER 29, 2005 FINAL OFFICE ACTION

Sir:

This Reply is being filed in response to the December 29, 2005 Final Office Action issued in the above-identified application. In that Office Action, a three-month shortened statutory period was set for response. Applicant hereby petitions for the necessary two-month extension of time[1] under 37 C.F.R. § 1.136(a)(2) to respond to that action and note that the fee required under 37 C.F.R. § 1.17(a) in connection with this extension of time will be paid during electronic filing via the Revenue Accounting and Management System. A Notice of Appeal is also being filed herewith. If it is determined that any additional fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this Reply, authorization to charge such fees to Deposit Account No. 02-2955 will be provided during electronic filing.

Please amend the above-identified application as follows:

A Listing of the Claims begins on page 2 of this paper.

Remarks begin on page 11 of this paper.

[1] With the two-month extension of time, the response to Final Office Action is due on or before May 29, 2006. However, because May 29, 2006 is a Federal Holiday, the response is due the next business day, i.e., on or before May 30, 2006, under 37 U.S.C. § 1.7.

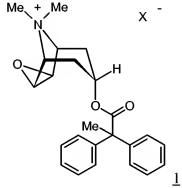
Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in this application:

Listing of Claims:

1. (previously amended) A pharmaceutical composition comprising:

(a) one or more anticholinergics of formula 1



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wherein:

X^- is an anion with a single negative charge; and

(b) one or more NK_1 receptor antagonists,

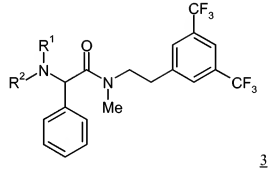
or an enantiomer, mixture of enantiomers, racemate, solvate, or hydrate thereof.

2. (previously amended) The pharmaceutical composition according to claim 1, wherein X^- is chloride, bromide, iodide, sulphate, phosphate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, 4-toluenesulphonate, or methanesulphonate.

3. (previously amended) The pharmaceutical composition according to claim 1, wherein X^- is bromide.

4. (previously amended) The pharmaceutical composition according to claim 1, wherein the NK_1 receptor antagonists are selected from BIIF 1149, CP-122721, FK-888, NKP 608A, CGP 60829, SR 48968 (Saredutant), SR 140333 (Nolpitantium besilate/chloride), LY 303870 (Lanepitant), MEN-11420 (Nepadutant), SB 223412, MDL-105172A, MDL-103896, MEN-11149, MEN-11467, DNK 333A, SR-144190, YM-49244, YM-44778, ZM-274773, MEN-

10930, S-19752, Neuronorm, DA-5018, MK-869, L-754030, CJ-11974, L-758298, DNK-33A, CJ-11974, TAK-637, GR 205171, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-{4-[(3-hydroxypropyl)methylamino]piperidin-1-yl}-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-[4-(2-hydroxy-1-hydroxymethylethylamino)piperidin-1-yl]-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-[4-(cyclopropylmethylmethylamino)piperidin-1-yl]-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-{4-[(2-hydroxyethyl)-(3-hydroxypropyl)amino]piperidin-1-yl}-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-{4-[cyclopropylmethyl-(3-hydroxypropyl)amino]piperidin-1-yl}-N-methyl-2-phenylacetamide, or an arylglycinamide compound of formula 3



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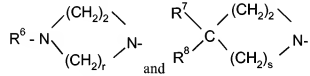
wherein:

R^1 and R^2 together with the N to which they are bound form a ring of formula



and

wherein r and s are each 2 or 3,

R^6 is H, -C_1-C_5-alkyl, C_3-C_5-alkenyl, propynyl, hydroxy(C_2-C_4)alkyl, methoxy(C_2-C_4)alkyl, di(C_1-C_3)alkylamino(C_2-C_4)alkyl, amino(C_2-C_4)alkyl, amino, di(C_1-C_3)alkylamino, monofluoro- to perfluoro(C_1-C_2)alkyl, N-methylpiperidinyl, pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl,

R^7 is one of (a) to (c),

(a) hydroxy,

(b) 4-piperidinopiperidyl,

(c)

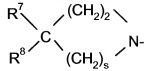
wherein R^{16} and R^{17} are each independently H, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_2-C_4)alkyl, dihydroxy(C_2-C_4)alkyl, (C_1-C_3)alkoxy(C_2-C_4)alkyl, phenyl(C_1-C_4)alkyl, or di(C_1-C_3)alkylamino(C_2-C_4)alkyl, and

R^8 is H,

or an enantiomer, mixture of enantiomers, or racemate thereof.

5. (previously amended) The pharmaceutical composition according to claim 1, wherein NK_1 receptor antagonists are selected from the group consisting of BIIF 1149, CP-122721, CGP 60829, MK-869, CJ-11974, GR 205171, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-{4-[(3-hydroxypropyl)methylamino]piperidin-1-yl}-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-[4-(2-hydroxy-1-hydroxymethylethylamino)piperidin-1-yl]-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)-ethyl]-2-[4-(cyclopropylmethylmethylamino)piperidin-1-yl]-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-{4-[(2-hydroxyethyl)(3-hydroxypropyl)amino]piperidin-1-yl}-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-{4-[cyclopropylmethyl-(3-hydroxypropyl)-amino]piperidin-1-yl}-N-methyl-2-phenylacetamide, or an arylglycinamide compound of formula 3, wherein:

R^1 and R^2 together with the N to which they are bound form a ring of formula



wherein s is 2 or 3,

R^7 is

wherein R^{16} and R^{17} are independently H, $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_2\text{-}C_4)$alkyl, dihydroxy$(C_2\text{-}C_4)$alkyl, $(C_1\text{-}C_3)$alkoxy$(C_2\text{-}C_4)$alkyl, phenyl$(C_1\text{-}C_4)$alkyl, or di$(C_1\text{-}C_3)$alkylamino$(C_2\text{-}C_4)$alkyl, and

R^9 is H,

or an enantiomer, mixture of enantiomers,or racemate thereof.

6. (previously amended) The pharmaceutical composition according to claim 1, wherein the NK_1 receptor antagonist is (S)-N-[2-(3,5-bis-trifluoromethylphenyl)ethyl]-2-[4-(2-hydroxy-1-hydroxymethylethylamino)piperidin-1-yl]-N-methyl-2-phenylacetamide or an acid addition salt thereof.

7. (previously amended) The pharmaceutical composition according to claim 1, wherein the weight ratio of the anticholinergic to NK_1 receptor antagonist is in the range from 1:100 to 100:1.

8. (previously amended) The pharmaceutical composition according to claim 1, wherein a single administration corresponds to a dosage of the combination of the anticholinergic and the NK_1 receptor antagonist of 0.01 μg to 10,000 μg.

9. (previously amended) The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in the form of a formulation suitable for inhalation.

10. (previously amended) The pharmaceutical composition according to claim 9, wherein the pharmaceutical composition is a formulation selected from inhalable powders, propellant-containing metering aerosols, and propellant-free inhalable solutions or suspensions.

11. (previously amended) The pharmaceutical composition according to claim 10, wherein the pharmaceutical composition is an inhalable powder which contains the anticholinergic and the NK_1 receptor antagonist in admixture with suitable physiologically acceptable excipients selected from the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients.

12. (previously amended) The inhalable powder according to claim 11, wherein the excipient has a maximum average particle size of up to 250 μm.

13. (previously amended) A capsule containing an inhalable powder according to claim 11 or 12.

14. (previously amended) The pharmaceutical composition according to claim 10, wherein the pharmaceutical composition is an inhalable powder consisting essentially of the NK_1 receptor antagonist.

15. (previously amended) The pharmaceutical composition according to claim 10, wherein the pharmaceutical composition is a propellant-containing inhalable aerosol comprising the anticholinergic and the NK_1 receptor antagonist in dissolved or dispersed form.

16. (previously amended) The propellant-containing inhalable aerosol according to claim 15, wherein the propellant gas is n-propane, n-butane, or isobutane, or chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane, or cyclobutane.

17. (previously amended) The propellant-containing inhalable aerosol according to claim 16, wherein the propellant gas is TG11, TG12, TG134a, TG227, or a mixture thereof.

18. (previously amended) The propellant-containing inhalable aerosol according to claim 15, further comprising one or more other ingredients selected from the group consisting of cosolvents, stabilizers, surfactants, antioxidants, lubricants, and means for adjusting the pH.

19. (previously amended) The propellant-containing inhalable aerosol according to claim 15, wherein the inhalable aerosol contains up to 5 wt.-% of the anticholinergic and/or the NK_1 receptor antagonist.

20. (previously amended) The pharmaceutical composition according to claim 10, wherein the pharmaceutical composition is a propellant-free inhalable solution or suspension which contains water, ethanol, or a mixture of water and ethanol as solvent.

21. (previously amended) The inhalable solution or suspension according to claim 20, wherein the pH range is 2 to 7.

22. (previously amended) The inhalable solution or suspension according to claim 21, wherein the pH is adjusted by means of an acid selected from among hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid, and propionic acid, or a mixture thereof.

23. (previously amended) The inhalable solution or suspension according to claim 20, further comprising other co-solvents and/or excipients.

24. (previously amended) The inhalable solution or suspension according to claim 23, wherein the co-solvents are isopropyl alcohol, propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols, or polyoxyethylene fatty acid esters.

25. (previously amended) The inhalable solution or suspension according to claim 23, wherein the excipients are surfactants, stabilizers, complexing agents, antioxidants and/or preservatives, flavorings, pharmacologically acceptable salts, or vitamins.

26. (previously amended) The inhalable solution or suspension according to claim 25, wherein the complexing agent is edetic acid or a salt of edetic acid, preferably sodium edetate.

27. (previously amended) The inhalable solution or suspension according to claim 25, wherein the antioxidants are ascorbic acid, vitamin A, vitamin E, or tocopherols.

28. (previously amended) The inhalable solution or suspension according to claim 25, wherein the preservatives are cetyl pyridinium chloride, benzalkonium chloride, benzoic acid, or benzoates.

29. (previously amended) The inhalable solution or suspension according to claim 23, consisting essentially of the anticholinergic, the NK_1 receptor antagonist, the solvent, benzalkonium chloride, and sodium edetate.

30. (previously amended) The inhalable solution or suspension according to claim 23, consisting essentially of the anticholinergic, the NK_1 receptor antagonist, the solvent, and benzalkonium chloride.

31. (previously amended) The inhalable solution or suspension according to claim 20, wherein the inhalable solution or suspension is a concentrate or a sterile ready-to-use inhalable solution or suspension.

32. (previously amended) A method of nebulizing the inhalable solution or suspension according to claim 20, wherein the inhalable solution or suspension is nebulized using an inhaler according to WO 91/14468 or an inhaler as described in Figures 6a and 6b of WO 97/12687.

33. (previously amended) The method of nebulizing an inhalable solution or suspension according to claim 31, wherein the inhalable solution or suspension is nebulized using an

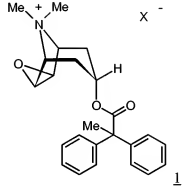
energy-operated free-standing or portable nebulizer which produces inhalable aerosols by means of ultrasound or compressed air.

34. (previously amended) The propellant-containing inhalable aerosol according to claim 17, wherein the propellant gas is TG134a, TG227, or a mixture thereof.

35. (currently amended) A method of treatment ~~and/or prevention~~ of ~~an inflammatory or obstructive~~ a disease selected from the group consisting of asthma, chronic obstructive pulmonary disease, pulmonary hypertension, allergic and non-allergic rhinitis, ~~of the respiratory tract~~ comprising administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to claim 1.

36. (previously amended) A kit comprising:

(a) a first container containing a first pharmaceutical formulation comprising one or more anticholinergics of formula 1



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wherein:

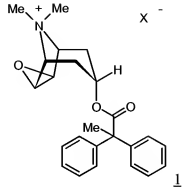
X^- is an anion with a single negative charge,

or an enantiomer, mixture of the enantiomers, racemate, solvate, or hydrate thereof; and

(b) a second container containing a second pharmaceutical formulation comprising one or more NK_1 receptor antagonists, or an enantiomer, mixture of the enantiomers, racemate, solvate, or hydrate thereof.

37. (previously amended) A method of treatment and/or prevention of an inflammatory or obstructive disease of the respiratory tract comprising administering simultaneously or

sequentially to a mammal in need of such a treatment a therapeutically effective amount of a first pharmaceutical formulation comprising one or more anticholinergics of formula 1



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wherein:

X^- is an anion with a single negative charge, and a second pharmaceutical formulation comprising one or more NK_1 receptor antagonists, each of the anticholinergic and the NK_1 receptor antagonist optionally in the form of an enantiomer, mixture of enantiomers, racemate, solvate, or hydrate thereof.

Remarks

Applicants acknowledge, with appreciation, the Examiner's withdrawal of the previous rejections under 35 U.S.C. 103(a).

Claims 1-37 are pending. Claim 35 has been amended to delete recitation of the term "and/or prevention of an inflammatory or obstructive disease of the respiratory tract," while reciting "a disease selected from the group consisting of asthma, chronic obstructive pulmonary disease, pulmonary hypertension, allergic and non-allergic rhinitis." Support for this amendment is found in the specification on page 10, lines 8-14. This amendment places claim 35 in better form for allowance or consideration on appeal.

The amendment set forth above does not introduce new matter.

A. The Prematurity of the Finality of the Office Action of December 29, 2005

Should the Examiner not now allow the application, applicants respectfully request that the Examiner withdraw the finality of the Final Office Action. On page 3 of the Final Office Action, the Examiner asserts that "Applicants' Amendment necessitated the new ground of rejection presented in this Office Action." However, in applicants' October 7, 2005 response, none of the claims were amended but instead, applicants made arguments directed to the Examiner's rejections. Moreover, it is not clear what new ground of rejection to which the Examiner is referring in the present Office Action. As the rejection was neither necessitated by applicant's amendment of the claims nor based on information submitted in an IDS filed after the first Office Action, the finality of the Final Office Action is improper and should be withdrawn. *See* M.P.E.P. § 706.07(c)-(d).

B. Rejoinder of Claims 9-34

The Examiner maintains that claims 9-34 of the present application are withdrawn from consideration under 37 C.F.R. § 1.142(b). However, pharmaceutical composition claims 9-34 are dependent directly or indirectly from independent pharmaceutical composition claim 1. If claim 1 is patentable over the prior art, then claim 9-34 should also be patentable over the prior art because the subject matter of claims 9-34 is narrower in scope than that of claim 1. Applicants respectfully requests that the Examiner rejoin claims 9-34 to

the remaining claims or that the Examiner explain more fully the propriety of her reasons for making narrower, dependent claims 9-34 the subject matter of a divisional application.

C. Rejection under 35 U.S.C. § 112, first paragraph

Claim 35 stands rejected under under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and practice the invention. The Examiner asserts that no support is provided for the combination for the prevention of any inflammatory or obstructive disease of the respiratory tract. The Examiner suggested that deleting the term "preventing" and providing specific disease would obviate the rejection. Applicants traverse.

While not agreeing with the propriety of the Examiner's rejection and solely to advance prosecution, applicants have adopted the Examiner's suggestion for claim 35, thus rendering moot the Examiner's rejection. Applicants reserve the right to file for and obtain claims directed to subject matter that has been cancelled from claim 35 in a continuing application claiming priority herefrom under 35 U.S.C. § 120.

D. Obviousness-type Double Patenting Rejections

The Examiner points out in the December 29, 2005 Final Office Action that applicants have elected to hold the obviousness-type double patenting rejections set forth in the last Office Action in abeyance. In the last Office Action, claim 37 stood provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/117,163 (hereinafter "the '163 application), in view of Pairet et al., U.S. Patent 6,620,438 (hereinafter "the '438 patent). In addition, claims 1-8 and 35-37 stood rejected as being unpatentable over claims 6-9, 11 and 21-24 of Meissner et al., U.S. Patent No. 6,706,726 (hereinafter "the '726 patent"), in view of the '438 patent. Applicants traverse.

While not agreeing with the propriety of the Examiner's rejection and solely to advance prosecution, a terminal disclaimer has been filed over the claims of the '438 patent, thus removing the double patenting rejection. However, applicants request withdrawal of the

obviousness-type double patenting rejections over the '163 application and the '726 patent for the following reasons.

According to MPEP 804(II)(B)(1), "[i]n determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is – does any ***claim*** in the application define an invention that is merely an obvious variation of an invention ***claimed*** in the patent [emphasis added]?" Here, the Examiner concedes that both the '726 patent and the '163 application lack NK_1 receptor antagonists in the claims. It is only through the combination of the "later" filed '438 patent with either the '726 patent or the '163 application does the Examiner mitigate this deficiency. Thus, the invention defined in the ***claims*** of the present application is not an obvious variation of the invention defined in the ***claims*** of either the '726 patent or the '163 application. Applicants respectfully request withdrawal of these rejections or that the Examiner cite authority supporting her position.

E. Conclusion

Applicants submit that all the pending claims are allowable and respectfully solicit a Notice of Allowance for all of the pending claims. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

Respectfully submitted,

/wendy petka/

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